Review Article

Roles of galectin-3 in metabolic disorders and tumor cell metabolism

Ying-Shuang Li[1], Xiao-Tong Li[1], Lu-Gang Yu[2], Lei Wang[1], Zhao-Yu Shi[1], Xiu-Li Guo[1]*

[1]*Department of Pharmacology, Key Laboratory of Chemical Biology (Ministry of Education), School of Pharmaceutical Sciences, Shandong University, Jinan 250012, PR China;*

[2] *Department of Gastroenterology, Institute of Translational Medicine, University of Liverpool, Liverpool L69 3GE, UK.*

*Correspondence should be addressed to

Xiu-Li Guo

No. 44 Wen Hua Xi Road, Department of Pharmacology, School of Pharmaceutical Sciences, Shandong University, Jinan 250012, P.R. China

Fax: +86-531-88382490

Telephone: +86-531-88382490

E-mail: guoxl@sdu.edu.cn

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Abstract

The galactoside-binding protein galectin-3 is commonly overexpressed by cancer cells and promotes cancer progression and metastasis. Over the past few years, evidence has emerged that galectin-3 is also overexpressed in several metabolic malfunction conditions such as diabetes, obesity and atherosclerosis and is involved in the regulation of the occurrence and development of these diseases. Recently, Galectin-3 expression is shown also to be associated with glycolysis and mitochondrial metabolism in tumors, and promotes tumor metabolic reprogramming for their adaption to the microenvironment stress imposed by oxygen and nutrients deprivation. This brief review summarizes the current understanding of the roles and actions of galectin-3 in these metabolic diseases and in tumor metabolism.

Keywords

Galectin-3; Metabolic disorders; Tumor metabolism

1. Introduction

Maintaining an adequate and balanced metabolism is essential in tissue homeostasis [1]. Malfunction of cell metabolism can trigger a number of metabolic disorders such as diabetes, obesity and atherosclerosis. Tumor cells are usually adapted to various extreme microenvironments and perform metabolic reprogramming to meet their rapid need of growth [1,2]. Over the past years, cell expression of the galactoside-binding protein galectin-3 is shown to be associated with several metabolic diseases such as diabetes, obesity and atherosclerosis (AS) [3-8].

Galectin-3 (also known as Mac-2, IgE-binding protein, L-29 or CBP30) is a 29-35kDa β-galactoside-binding protein [9]. It has a highly conserved β-galactoside binding domain (carbohydrate recognition domain, CRD) and an extended N-terminal domain [9,10]. Galectin-3 is widely expressed by immune cells and epithelial cells. It

is synthesized in the cytoplasm and shuttles between the cytoplasm and the nucleus. It can also be secreted into the cell membrane and extracellular fluid as a soluble protein [11].

In diabetes mellitus, galectin-3 expression has been reported to be involved in insulin resistance and glucose intolerance [8,12]. Galectin-3 is also shown to be involved in lipid metabolism disorders and adipose tissue dysfunction in obesity [8,13]. Galectin-3 expression is involved in the occurrence and development of AS and has been investigated as a possible target for prevention of AS-associated cardiovascular and cerebrovascular diseases [14,15]. More recently, galectin-3 was reported to participate in cell glycolysis and mitochondrial metabolism in some tumors [16-19]. In this review, we summarize the current understanding of the involvment of galectin-3 in these metabolic diseases of diabetes, obesity, and atherosclerosis, and in tumor cell metabolism.

2. The structure of galectin-3

The galectin family members are divided into three types according to the molecular architecture: (1) the prototype which are usually homodimers containing one carbohydrate recognition domain (CRD) in each subunit; (2) the tandem-repeattype which are monomers containing two CRDs connected by a linker region; (3) the chimeratype containing a C-terminal CRD connected to a large repeating sequence and an N-terminal domain [20]. Among them, galectin-3 is the only chimera galectin with three domains: (1) a short N-terminal unique region of 12 amino acids (aa) containing a serine phosphorylation site for the control of cell targeting; (2) a collagen-like sequence of 100aa comprising tandem repeats of proline, glycine and tyrosinel, which contains the collagenase cleavable H-domain, in which histidine 64 is the site of action of matrix metalloproteinases (MMPs) such as MMP9 and MMP2; (3) a spherical C-terminal CRD domain containing the Asp-Trp-Gly-Arg (NWGR) motif, similar to those described in anti-apoptotic Bcl-2 proteins [21] (Fig. 1). Intracellular galectin-3 regulates pre-mRNA splicing, cell proliferation, differentiation, and apoptosis through oligomerization at the N-terminus, while

extracellular galectin-3 recognizes β-galactosides on the cell surface or extracellular matrix to exert the immune regulation, cell adhesion, anti-apoptosis and nuclear transport mainly through its C-terminus [10,21].

3. The expression of galectin-3 in patients with diabetes, obesity or atherosclerosis

Compared to normal people, the expression level of galectin-3 is upregulated in obese people and patients with type 2 diabetes mellitus (T2DM) without gender differences [22]. The level of serum galectin-3 in diabetic patients is significantly elevated than that in people with impaired glucose tolerance and normal blood glucose [8,22]. In addition, there are more macrophages in diabetic patients, leading to upregulated expression and massive accumulation of galectin-3 in the kidneys and cardiovascular system, moreover, the expression of galectin-3 tends to continuously increase along with the progression of the disease [22,23]. Furthermore, compared to normal mice, the expression levels of galectin-3 are upregulated in liver, subcutaneous and visceral adipose tissues of obese mice [47]. With respect to atherosclerosis, the expression levels of galectin-3 are upregulated in plasma and atherosclerotic plaques of both diseased mice and humans compared with the normal individuals, and the galectin-3 level is positively correlated with the severity or instability of plagues in the plasma of patients with atherosclerosis [24].

4. Galectin-3 in diabetic metabolism

Several studies have reported the galectin-3 involvement in glucose metabolism in mice [25]. Fed with a high-fat diet, galectin-3 knockout (KO) mice showed to have higher levels of fasting blood glucose, insulin, and HbA1c compared to the normal control mice [26]. The galectin-3 KO mice expressed lower level of glucose transporters than the control mice, which was speculated to contribute to the higher blood glucose level in the KO mice [26]. Morever, it was proposed that young galectin-3 KO mice, which were physiologically less able to cope with high glucose loads, would suffer from mild hyperglycemia with aging and aided further

development of obesity and systemic inflammation compounded by high-fat feeding [27]. Galectin-3 expression increased the glucose transport and uptake in fat cells by promoting the expression of glucose transport 4 (GLUT4) and its transport to the cell membrane, so as to maintain the blood glucose level within a normal range [28]. The study also found that galectin-3 expression helped to repair endothelial injury and metabolic dysfunction caused by diabetes [28]. Several studies have reported the galectin-3 was involved in the regulation of advanced glycosylation end products (AGEs) and lipid peroxidation end products (ALEs) in diabetes [29]. The accumulation of AGEs/ALEs in the body was one of the pathogenesis of diabetic chronic complications, and was proved to aggravate the vascular injury in diabetic patients [8,30]. Galectin-3 was shown to accelerate AGEs/ALEs degradation and prevent tissue damage in the kidney and blood vessels, whereas galectin-3 would lead to accelerated tissue damage in the liver, because of its ability to slow down AGEs/ALEs degradation [8,29]. It was assumed that the variation in the effect in different organs was due to the unique catabolism of AGEs/ALEs in the liver [31,32]. Galectin-3 expression could promote AGEs/ALEs uptake by hepatic sinus endothelial cells and kupffer cells, which cause the overload of the detoxification system and activation of the AGE-RAGE signaling pathway, triggering nonalcoholic steatohepatitis [8,31,32].

Galectin-3 may cause insulin resistance in certain stages of diabetes, such as obese prediabetes. It was shown that endogenous galectin-3 could reduce glucose tolerance and insulin sensitivity in muscle cells, hepatocytes and adipose cells, while exogenous galectin-3 would lead to insulin resistance in the above cells [33,34]. Galectin-3 was proved to act directly on all the three major target organs of insulin: inhibiting the uptake of glucose by muscle cells and adipose cells under insulin stimulation, and reducing the inhibitory effect of insulin on the glucose secretion of mouse hepatocytes [34,35] (Fig. 2). Moreover, galectin-3 was shown to bind to the oligosaccharide side chain of insulin receptor (IR) to prevent insulin binding to IR, thus inhibiting insulin-mediated receptor activation [34] (Fig. 3). Galectin-3 secretion into the blood and other body fluids from bone marrow-derived macrophages caused cellular and

systemic insulin dysfunction in the body [34]. In obese mice, depletion of galectin-3 expression through genetic approaches or administration of galectin-3 binding inhibitors could restore insulin sensitivity and glucose tolerance [35]. These discoveries indicate that galectin-3 may represent a pathogenic factor of insulin resistance and chronic tissue inflammation in obesity and a potential metabolic target to prevent or reverse insulin resistance.

Interestingly, compared with mothers without gestational diabetes, mothers with the clinical presentations and their neonates were showed to have higher galectin-3 level in cord blood [36], suggesting that the clinical relevance of galectin-3 in diabetes may be associated with specific diabetic conditions. The role of galectin-3 in promoting placental angiogenesis may explain why women with gestational diabetes always give birth to neonates of large gestational age [36-38].

5. Galectin-3 in fat metabolism and obesity

Obesity is a metabolic disorder associated with exacerbated inflammation in adipose tissue, which may be caused by higher levels of inflammation cytokines, such as TNF-α, IL-6 and IL-1β [39]. Galectin-3 has been shown to be an inflammatory regulator in obesity and insulin resistance (Table 1).

Galectin-3 is shown to have multiple influences on fat metabolism, e.g. in adipocyte anabolism and catabolism. In adipocyte anabolism, galectin-3 showed to promote the production of pro-inflammatory molecules, stimulate proliferation of fibroblasts, and inhibit the activity of adipose triglyceride lipase (ATGL) [40]. In the white adipose tissue of the epididymis (eWATs) of galectin-3 knockout mice, levels of adipocyte expression-associated genes peroxisome proliferator-activated receptor (PPAR)-γ, fatty acid binding protein 4 (FABP4) and fatty acid synthase (FAS) were significantly reduced in the liver [27]. Administration of 10^{-8} mol/L exogenous galectin-3 increased the preadipocytes fibrosis and inflammation in 3T3-L1 cells [41], while the expression of endogenous galectin-3 stimulated the differentiation of 3T3-L1 cells into mature adipocytes by activating PPAR-γ [41,42]. In contrary, treatment of Hela cells with exogenous galectin-3 showed to activate ERK1/2

signaling pathways that reduced PPAR-γ and C/EBPα expression and inhibited fat anabolism [43]. Galectin-3 expression also inhibited GSK-3β activity and β-catenin phosphorylation thereby decreasing fat anabolism and adipocyte differentiation [44,45]. Jeftic et al. reported that several obesity-associated transcription factors such as PPAR-γ, animal body weight, and visceral adipose tissue were increased in galectin-3 knockout mice fed with high-fat diet compared to wild-type mice [46]. In addition, high expression of galectin-3 mediated by IL-6 and FFA was reported to promote adipocyte catabolism in adipocyte tissue [47].

Two of the most typical metabolic changes in obesity are insulin resistance and cardiotoxicity (lipid deposits in the heart). Higher level of galectin-3 in the blood circulation was observed in human and rodent with obesity [48,49]. Galectin-3 was highly expressed in the visceral adipose tissue and subcutaneous adipose tissue of obese mice fed with high fat diet [26]. It was also proposed that higher galectin-3 level in blood circulation of obese rats was associated with higher serum levels of triglyceride (TG) and lysophosphatidyl choline (LPC) [49], which might cause lipotoxicity and aggravate severe metabolic disorders.

Studies in mice suggested galectin-3 was a positive regulator of high-fat diet-induced obesity. 6-week-old galectin-3 knockout mice fed with high-fat chow (60% fat) for 12 weeks had lower body weight and eWAT level compared to the wild-type mice received the same diet [27]. Administration of galectin-3 inhibitor modified citrus pectin (MCP) to high-fat diet rats could decrease the level of carnitine palmitoyltransferase I A (CPTIA), which is an important molecule in the mitochondrial outer membrane that catalyzes the rate-limiting step of fatty acid oxidation (FAO) [49,50].

Galectin-3 was shown to bind to lipopolysaccharides and negatively regulate the production of inflammatory cytokines in macrophages [41,51]. It can also promote chemotaxis of monocyte-macrophages and the production of inflammatory factors in adipose tissue [52] (Fig. 3). Administration of the galectin-3 inhibitor MCP was proposed to effectively reduce the inflammatory responses and adipocyte differentiation in obese mouse models, and alleviated obesity-induced cardiac

dysfunction and myocardial fibrosis [3,53]. Martínez-Martínez E et al. demonstrated that galectin-3 mediated insulin resistance in obese mice could be associated with the activation of osteopontin (OPN), an early T-lymphocyte activator, and chemokine CCL2 [41]. The pro-inflammatory activity of galectin-3 has been linked to cardiac inflammation in obese patients and subsequent mitochondrial dysfunction in heart metabolism [54,55].

Together these studies indicate that galectin-3 is likely involved in the regulation of obesity and related metabolic complications through multiple mechanisms including regulating the expression of pro-inflammatory cytokines in fat anabolism or catabolism.

6. Galectin-3 in atherosclerosis

In atherosclerosis (AS), a layer of atherosclerosis materials including cholesterol crystals formed on the arterial wall, reduces arterial elasticity and narrows the lumen [56]. This often leads to threatening conditions such as coronary heart disease, cerebral infarction and peripheral vascular disease [57]. A number of studies have demonstrated the involvement of galectin-3 in the occurrence and development of AS (Fig. 4), and suggested galectin-3 to be a potential therapeutic target for the prevention or management of cardiovascular and cerebrovascular diseases induced by AS [14,15,58].

Oxidized low-density lipoprotein (Ox-LDL)-induced endothelial cell injury is known to play a crucial role in AS pathogenesis. Galectin-3 was shown to bind to integrin and induce β1-RhoA-JNK signaling that induces inflammation and ox-LDL-mediated endothelial injury [59]. Galectin-3 can also bind directly to low-density lipoprotein (LDL), inhibiting the adhesion of vascular smooth muscle cells (VSMCs) to matrix glycoproteins, thereby promoting the formation of atherosclerotic plaques [59-61]. In addition, galectin-3 was also reported to increase the lipid absorption of vascular endothelial cells and macrophages by activating Ox-LDL [60].

The pro-inflammatory activity of galectin-3 is also believed to participate in the

progression of atherosclerosis (AS) [59,62]. Galectin-3 expression induces secretion of pro-inflammatory molecules such as cytokines to accelerate interaction of inflammatory cells with endothelial cells, leading to vascular wall damage and elevation of the severity of atherosclerosis [62]. Galectin-3-mediated secretion of chemokines from macrophages and vascular endothelium also contributed to the enhancement of VSMCs and monocytes aggregation in arterial plaque lesions [62,63]. Galectin-3 secreted by activated macrophages promotes the differentiation of monocytes into macrophages, which can aggregate and adhere to the vascular wall and accelerate the formation of fat-laden macrophages (foam cells) [64]. Moreover, secretion of galectin-3 can induce proliferation of fibroblasts and the deposition of type I collagen in the extracellular matrix to promote tissue fibrosis and aggravate AS [65]. Galectin-3 can also aggravate the damage of pathological blood vessels during the formation of AS by enhancing the oxidative stress response of neutrophils and monocytes [66].

Sortilin (a sorting receptor) is a key factor of glucose and lipid metabolism disorders, often acting as an initiating factor for AS and vascular calcification. Previous study found that galectin-3 could promote the expression of sortilin, thus inducing micro-calcification in type 2 diabetic patients [67]. Anyfanti et al. indicated that higher level of galectin-3 was strongly associated with an increased risk of systemic vascular resistance (SVR) and decreased total arterial compliance in RA patients [68]. Significant associations were also identified between galectin-3 expression and central systolic blood pressure, peripheral pulse pressure as well as central pulse pressure [68].

7. Galectin-3 in tumor cell metabolism

7.1 Galectin-3 is involved in tumor metabolic reprogramme

In comparison to normal cells, tumor cells undergo "metabolic reprogramme" to meet its need of fast growth [69]. The dependence on glucose uptake and utilization is significantly enhanced in tumor cells compared with normal cells [69,70]. Even in an oxygen-rich microenvironment, tumor cells are more prone to glucose metabolism

through glycolysis rather than oxidative phosphorylation of glucose, a phenomenon known as "Warburg effect" [71,72]. Fatty acid oxidation is also an important metabolic pathway in tumor tissue and becomes more important in the extreme environment of glucose deprivation [73]. Abnormal energy metabolism is now considered one of the tumor characteristics [74]. The expressions of several molecules in metabolic pathways such as glucose transporter1 (GLUT1), hexose kinase (HK), phosphofructokinase (PFK), lactate dehydrogenase-A (LDHA), glutaminase 1, pyruvate kinase M2 subtype (PKM2), HIF-1, AMPK, mTOR and isocitrate dehydrogenase (IDH), are changed in tumor [73,75] and some of the changes have been reported to be regulated by galectin-3 (Fig. 5). In addition, galectin-3 could promote tumor metastasis mainly in an AKT-dependent manner to involve in metabolic reprogramme of different epithelial cancer cells and sarcomas [76].

Glucose transporters (GLUTs) are a family of transmembrane glycoproteins responsible for glucose uptake on the cell membrane. GLUT1, also known as solute carrier family 2 and a promoter of Warburg effect in tissue metabolism, is one of the most widely distributed GLUTs and has been shown to be abnormally activated in various cancers, such as liver, breast, esophageal, gastric, and lung cancer and adrenocortical carcinoma [77,78]. GLUT1 expression in cancer cells is regulated by a variety of factors, including hypoxia inducible factor-1α (HIF-1α), P53, gene of phosphate and tension homology deleted on chromsome ten (PTEN), peroxisome proliferators-activated receptor γ (PPARγ), vascular endothelial growth factor (VEGF), microRNAs (miR-132, miR-144, miR-150) and PI3K/AKT/mTOR singalling [79,80]. Galectin-3 was shown to be co-expressed with GLUT1 in breast tumors and lung cancer and both galectin-3 and GLUT1 expression were up-regulated in hypoxic tumor cells surrounding the necrotic areas [16]. Interesting, overexpression of GLUT1 and decreased expression of galectin-3 in endometrioid and serous carcinomas of the endometrium both were suggested to be indicators of malignant transformation of endometrial cancer epithelium [81,82]. In tumor cells, galectin-3 overexpression, associated with HIF-1α activity and glutaminolysis promoter p53 [19,83], increases PI3K signaling to promote GLUT1-mediated aerobic glycolysis of tumor [18,76,84].

In addition, galectin-3 expression can promote Ras and Erk activation to upregulate GLUT1 expression and the enzymatic activities of HK, PFK and LDHA [1,43,71,83,85,86].

7.2 Galectin-3 is involved in tumor mitochondrial metabolism

There is evidence that Galectin-3 is involved in maintaining mitochondrial homeostasis [87]. After synthesis, galectin-3 can translocate to the mitochondria membrane and interact with Bcl-2, resulting in inhibition of mitochondria cytochrome c release and reduction of cell apoptosis [87]. Suppression of galectin-3 expression reduced epirubicin-induced expression of ATP binding cassette transporters and increased the mitochondrial apoptosis pathway in colorectal carcinoma [88]. Galectin-3 expression can decrease cell production of reactive oxygen species (ROS) by increasing glutathione S-transferase (GST) expression [17]. It can also change molecule transport cross the mitochondrial membranes by altering mitochondria membrane permeability [17,89]. Galectin-3 expression was reported to be associated with the expressions of a few key mitochondrial metabolism regulatory proteins, such as AMPK and PPAR in cancer [90,91]. AMPK and PPAR are indicators of fatty acid oxidation in the mitochondria, and their activities affect the metabolic balance in tumors [81,90,91].

In addition, inconsistent patterns of galectin-3 were observed in different tumors, which were assumed to be due to the variation in the expression or the cellular location of galectin-3 in different tumor cells. For instance, a number of previous studies in epithelial ovarian carcinoma, colon cancer, prostate cancer, breast carcinoma, pancreatic carcinoma and liver cancer indicated that intracellular galectin-3 could maintain the mitochondrial homeostasis, while extracellular galectin-3 could bind to the glycoproteins CD29 and CD7 on the surface of T-cell lymphoma and send apoptosis signals to mitochondria [25,76,88,92].

7.3 Galectin-3 helps tumor cells to adapt metabolic stress

One of the key features in metabolism of tumor cells, that distinguishes them from

normal tissues, is their far higher energy consumption rate which often exceeds the available energy supply [69,71]. Nutrient depletion and necrosis are common features in tumor and inhibition of cell metabolism by nutrient deprivation has been proposed as a possible approach to kill tumor cells [93]. Under hypoxia and nutrient deprivation condition, the expression of galectin-3 in human glioblastoma multiformes T98G cells was seen to be significantly increased [94]. Ikemor and colleagues have reported that galectin-3 might be a regulator in tumor transplantation and growth under hypoxia and nutrient deprivation [94]. They showed that knocking out galectin-3 expression in hybrid human/murine NG97ht glioblastoma cells had no significant effect on cell survival under simple hypoxic conditions. However, under hypoxia as well as serum deprivation condition, galectin-3 knocking out resulted in a dramatic increase in tumor cell death [94]. The different effects on cell death caused by the presence or absence of serum under hypoxic condition supports the involvement of galectin-3 in the metabolic pathways of tumor cells. Galectin-3 overexpression may therefore promote transformation of cell metabolism from oxidative phosphorylation to glycolysis in tumor, and, by doing so, it aids tumor cells to adapt the metabolic stress.

Galectin-3 overexpression also showed to enhance tumor adaptation to hypoxic microenvironment by promoting angiogenesis, which in turn increases homeostasis of hypoxic and nutrient-deficient tissue microenvironment [37,94]. Galectin-3 can regulate vascular signaling programs through binding to integrin αvβ3 or by sustaining the pro-angiogenic capacity of tumor-associated macrophages (TAMs) [25,95]. Moreover, previous study in melanoma cells reported that extracellular galectin-3 could activate the p38 MAPK pathway thus inducing the expression of MMP-9, which could provide nutrient conditions for tumor angiogenesis together with VEGF [76,96]. These discoveries suggest that galectin-3 overexpression in tumor may represent an adaptive metabolism mechanisms for tumor to maintain cell viability and hemostasis in the stressful tumor microenvironment with deficiency of oxygen and nutrition.

Metabolic stress is known to speed up the competition between immune cells and tumor cells for nutrients such as glucose. Recent studies have shown that

tumor-secreted galectin-3 could hijack IFN-γ in the tumor microenvironment and reduce induction of a chemokine gradient of the CXCL9/10/11 and thus decrease T-cell recruitment into the melanoma [97]. Galectin-3 can bind to cell surface glycoproteins CD45 and CD71 to induce T cell death [98]. Collagen deposition in extracellular matrix enhanced by galectin-3 showed not only significantly to increase glutamate-driven tricarboxylic acid cycle in melanoma cells, but also to prevent T cell infiltration into tumor [98]. A study by John et al. also suggested galectin-3 expression essential for IgE-dependent activation of human basophils in A549 lung epithelial cells [99]. These studies indicate that galectin-3-mediated tumor cell-adaption under metabolic stress may help tumor evasion of the immune surveillance.

Furthermore, galectin-3 was seen to be highly expressed in the nutrition-deficient and hypoxic regions in the tumor [94] where TAMs were heavily accumulated [100]. Like tumor cells, TAMs are known to express and secrete large quantities of galectin-3 under certain conditions and also have high glycolysis activity [101]. Oral administration of galectin-3 antagonist GB1107 led to TAMs reversal from M2 phenotype to M1 phenotype and increased infiltration and activity of CD8+ cytotoxic T lymphocytes (CTLs) in human and mouse Lewis lung carcinoma [102]. It was reported that higher level of galectin-3 expression was correlated with increased sensitivity to immunotherapy of anti-PD-1 or anti-PDL1 among patients with non-small cell lung cancer (NSCLC) [102,103]. Moreover, single administration of galectin-3 inhibitors was shown to significantly inhibit the progression of lung cancer, which suggested that galectin-3 might contribute to the immune escape of tumor cells by promoting the interaction between the PD-L1 on tumor cells and the PD-1 on T cells, thus inhibiting the development and metastasis of lung adenocarcinoma [102-104]. Given its multiple roles in macrophages and T cells activity, secreted galectin-3 can regulate immune cells in the tumor microenvironment to help tumor cell adaptation to the metabolic stress and hence promote tumor progression (Fig. 6).

Tumor cells have the tendency to migrate to adipocyte-rich tissues and adipocytes can increase dependency on extrinsic lipid uptake in tumor cells [105]. For example, melanoma cells can actively absorb lipids in place of glucose, and the “fat-eating”

melanoma cells showed to have enhanced ability to chew collagen and cross-membrane [105]. Adipose tissue can also fuel tumor metastasis by secreting extracellular vesicles, which modulatie functions of distant tumor cells and tissues in a paracrine fashion [106]. Galectin-3, expressed by both macrophages and adipocytes, promotes adipocyte differentiation in adipose tissue [40]. Recent studies have suggested a link between galectin-3 expression/secretion and adipocytes functions [27,40,41,107]. Galectin-3 expression led to adipocytes enlargement and increased the lipid storage capacity of adipose tissue, thereby enhancing the metabolic plasticity of adipose tissue [40,107]. Galectin-3 secreted by adipocytes showed to act as an external factor such as within exosomes to help adipocytes communicate with tumor cells in the microenvironment [40,104,108].

Together, these recent indicate that galectin-3 can regulate adipocyte anabolism and catabolism through multiple mechanisms. Galectin-3 secreted by adipocyte-rich tissue might be an important player in promoting tumor response to metabolic stress imposed by deprivation of glucose and other nutrients (Fig. 6).

Conclusion

Galectin-3 is often overexpressed in metabolic diseases such as diabetes, obesity and atherosclerosis. There is good evidence of a relationship between galectin-3 overexpression and the occurrence and development of these diseases caused by glucose and lipid metabolic disorders. Galectin-3 overexpression enhances insulin resistance in obese prediabetes, adipose tissue dysfunction in obesity, and the severity of AS. There is however also evidence showing that galectin-3 expression can delay the progression of diabetes and obesity by maintaining blood glucose homeostasis and improving lipid metabolism disorders. The different roles of galectin-3 in diabetes and obesity may depend on its organ localization or the diseases' stage. This suggests that galectin-3 inhibitors may be potentially used to target specific organs or tissues in specific stages of diabetes or obesity. Galectin-3 overexpression is also associated with tumor cell glycolysis and mitochondrial metabolism and promotes tumor metabolic reprogramming for tumor adaptation to the microenvironment stress

imposed by oxygen and nutrients deprivation. Much still remains unknown of the molecular mechanisms of galectin-3 involvements in the metabolic processes of these diseases. Given the seemingly broad influence of galectin-3 on metabolic diseases, it is possible that further studies may help to turn galectin-3 into a diagnostic or therapeutic target for these diseases.

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Figure legends

Fig. 1. Structure of galectin-3. A. Galectin-3 monomer; **B.** Galectin-3 dimerization through its C-terminus in the absence of binding ligand and polymerization through its N-terminus in the presence of carbohydrate binding ligands.

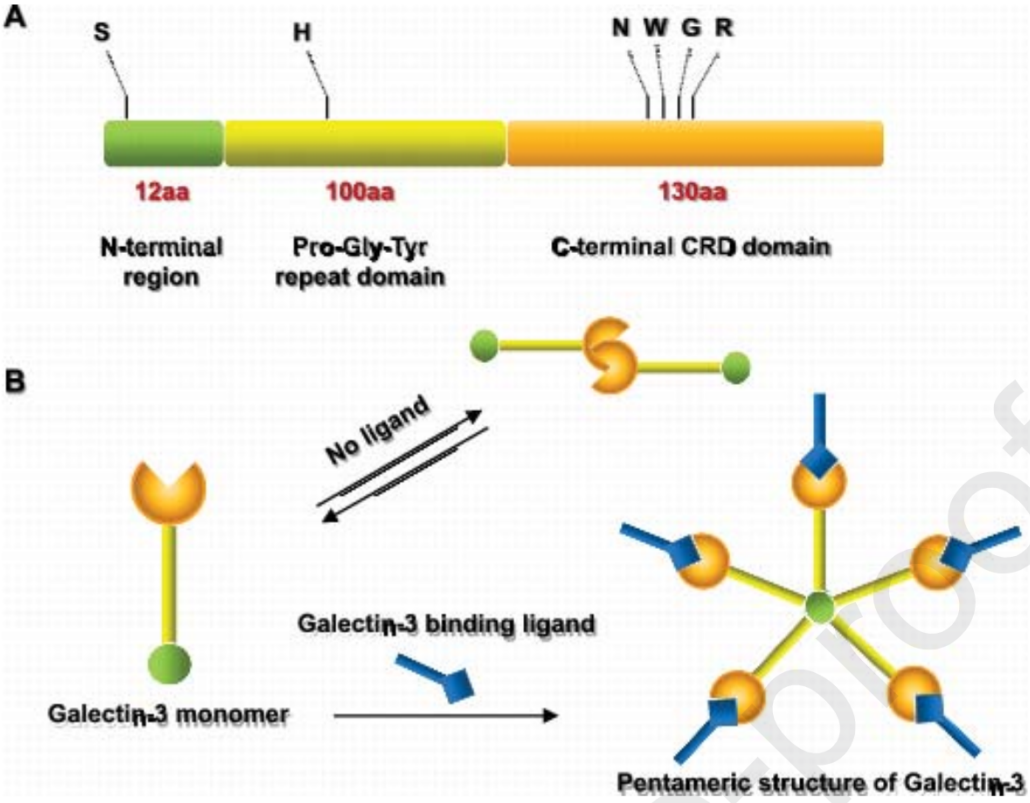
Fig. 2. Galectin-3 inhibits insulin binding to insulin receptor (IR) to cause hyperglycemia. Galectin-3 showed to directly induce insulin resistance in three important insulin target tissues to cause hyperglycemia in obese prediabetes: **(1)** inhibiting the uptake of glucose by muscle cells and adipose cells under insulin stimulation, and **(2)** reducing the inhibitory effect of insulin on the glucose secretion of hepatocytes.

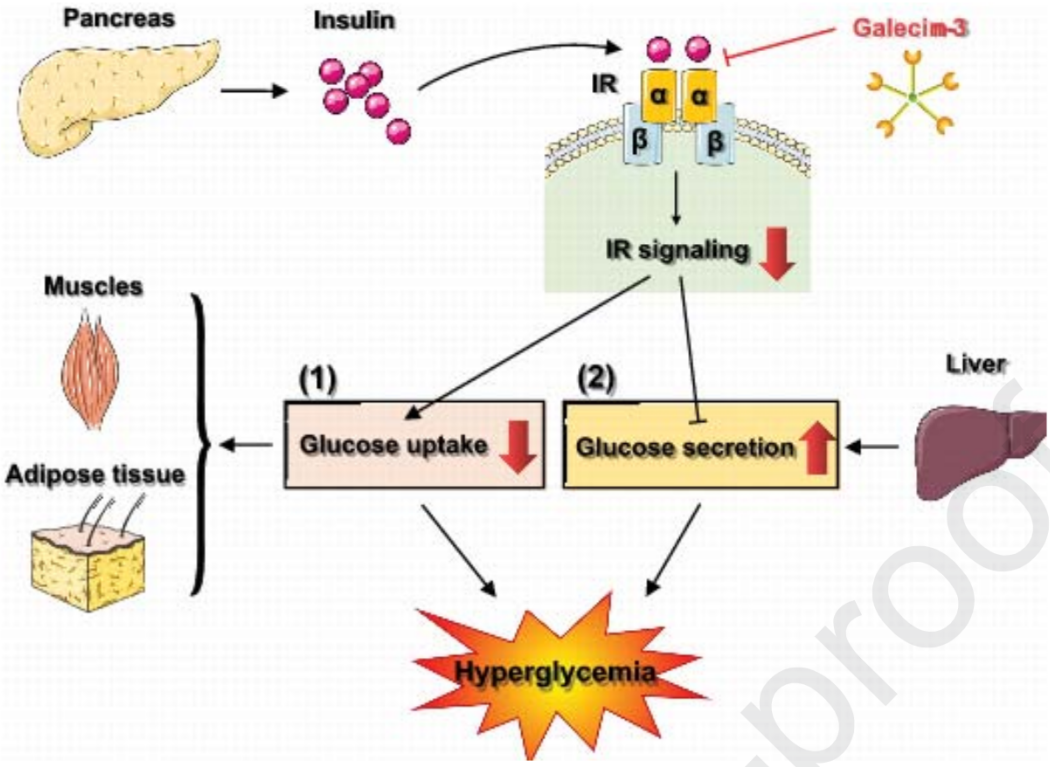
Fig. 3. Galectin-3 produced by inflammatory macrophages perpetuates obesity-induced insulin resistance. Galectin-3 caused insulin resistance by dual effects on the IR directly and tissue inflammation. **A.** Galectin-3 exerts its insulin desensitizing effects by directly binding to the oligosaccharide side chain of insulin receptor (IR) that is distinct from the insulin binding domain, which leads to abrogation of insulin receptor signaling and glucose transporter 4 (GLUT4) translocation. **B.** Galectin-3 causes macrophage chemotaxis and continuous recruitment of monocytes from the circulatory system by adipose tissue, promoting the differentiation of monocytes into inflammatory macrophages.

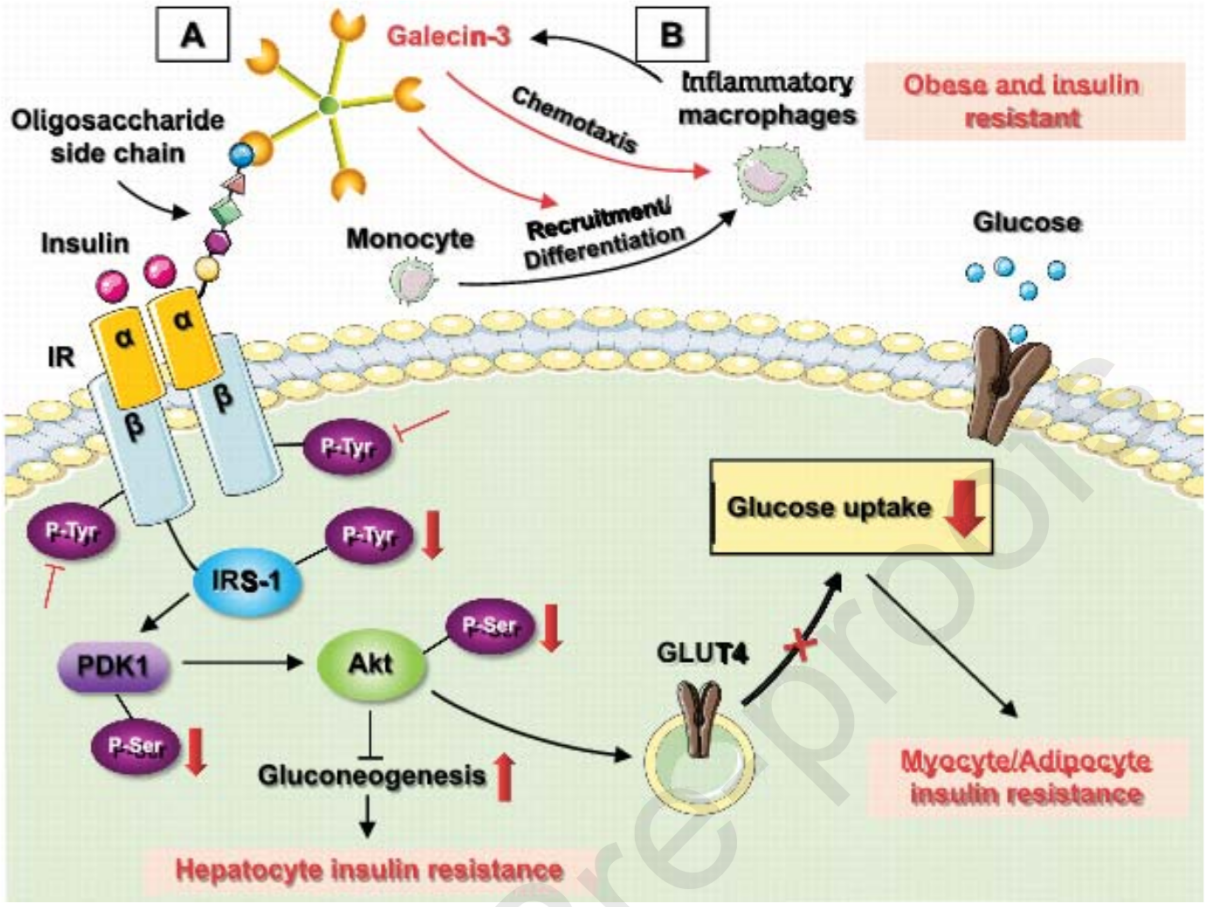
Fig. 4. Role of galectin-3 in atherosclerosis (AS). The involvement of galectin-3 in AS includes: **(1)** exacerbating oxidized low-density lipoprotein (Ox-LDL)-induced endothelial injury by inducing inflammation via integrin β1-RhoA-JNK signaling activation; **(2)** enhancing the oxidative stress response of neutrophils and monocytes; **(3)** promoting the differentiation of monocytes into macrophages, which are the main cells in the inflammatory response of AS; **(4)** accelerating the formation of foam cells which are lipid-loaded macrophages generated from the massive uptake of modified low-density lipoproteins; **(5)** promoting the metastasis of vascular smooth muscle cells (VSMCs) from the media to the intima; **(6)** promoting the hyperplasia of VSMCs; **(7)** promoting the chemokine production from macrophages by its inflammatory properties; **(8)** accelerating the deposition of collagen in the intima and tissue fibrosis; **(9)** regulating cell apoptosis to increase plaque instability. The dotted arrow indicates putative roles of galectin-3 that needs further investigation for confirmation.

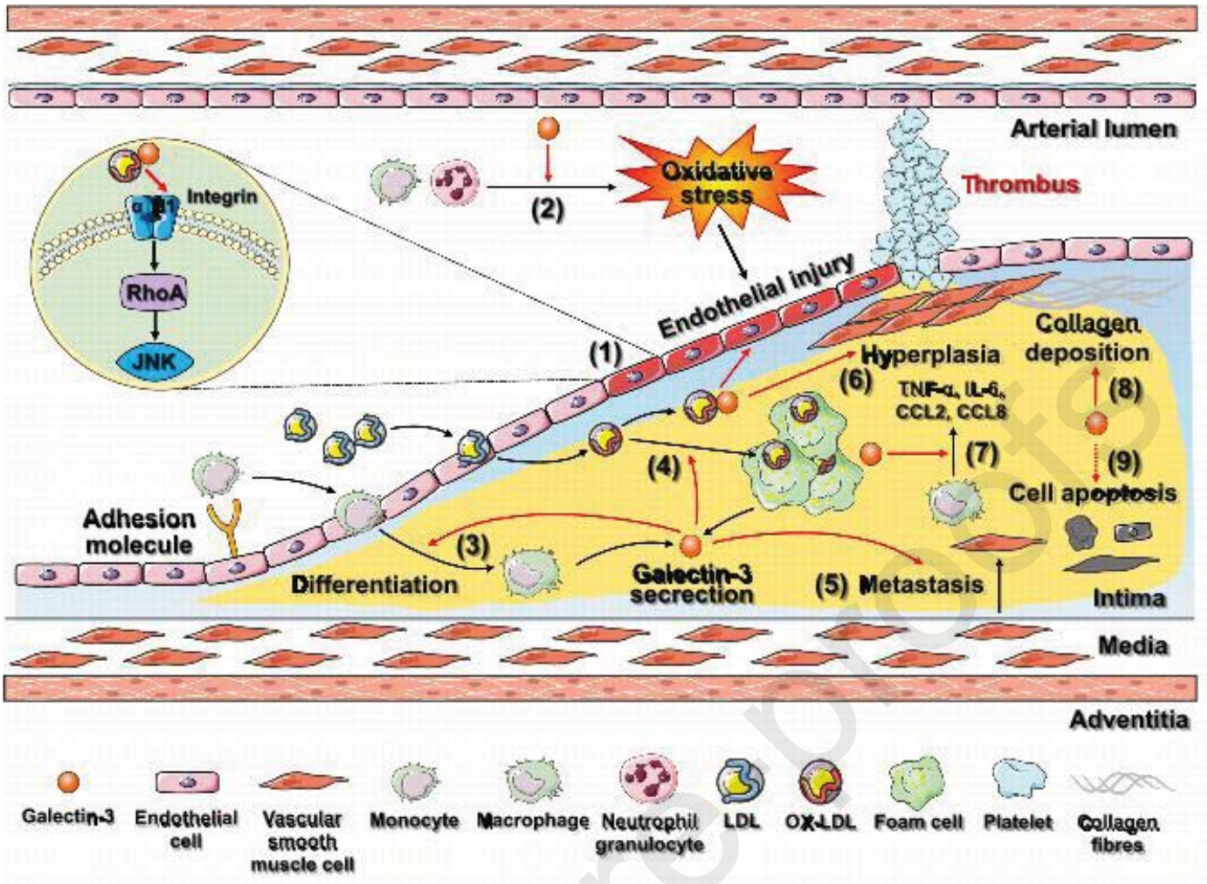
Fig. 5. Role of galectin-3 in the metabolic pathways of tumor cells away from blood vessels. The expression level of galectin-3 in hypoxic regions is higher than that in oxygen-rich regions. The involvement of galectin-3 in tumor metabolic pathways includes: **(1)** Galectin-3 overexpression can upregulate the GLUT1 expression directly or indirectly by K-Ras or c-Myc; **(2)** Galectin-3 increases PI3K signaling, which can activate HK, PFK and GLUT1 to promote aerobic glycolysis; **(3)** The high expression of galectin-3 in hypoxia and nutrient-deficient regions is associated with HIF-1α, which can activate LDHA to accelerate lactic acid production; **(4)** Galectin-3 may affect fatty acid oxidation (FAO) by regulating PPAR-γ; **(5)** Galectin-3 can maintain mitochondrial homeostasis by inhibiting the generation of ROS and the release of cytochrome C, as well as **(6)** promoting mitophagy and other catabolic reactions. The dotted arrow indicates putative roles of galectin-3 that needs further investigation for confirmation.

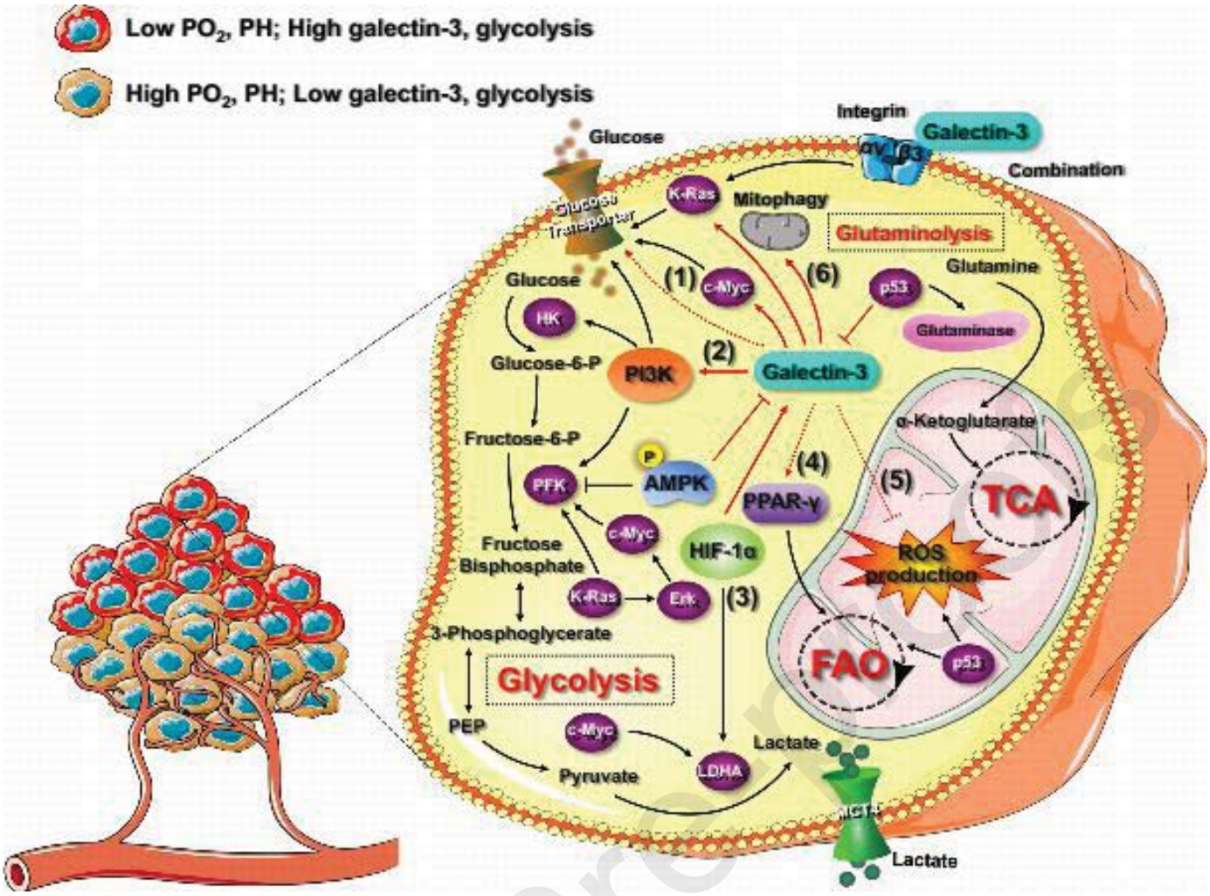
Fig. 6. Role of galectin-3 in metabolic changes of tumor cells and immune cells in tumor extracellular matrix (ECM) and adipocyte-rich tissue. A. Galectin-3 helps tumor cells to adapt immune microenvironment in ECM. **(1)** Binding of galectin-3 to cell surface glycoproteins reduces IFN-γ diffusion in ECM and inhibits T-cell infiltration; **(2)** Galectin-3 promotes interaction of PDL1 with PD1 to help tumors evade immune surveillance; **(3)** T cell dysfunction caused by galectin-3 may weaken their ability to compete with tumor cells for glucose; **(4)** Galectin-3 secretion contributes to the collagen deposition, which can increase glutamate-driven tricarboxylic acid cycle to maintain tumor metabolic balance; **(5)** Galectin-3 promotes the differentiation of monocytes into tumor associated macrophages (TAMs). **B.** Role of galectin-3 secreted by adipocyte-rich tissue in tumor progress. **(6)** Secretion of galectin-3 and extracellular vesicles by adipocytes fuel tumor metastasis; **(7)** Galectin-3 secreted by adipocyte-rich tissue promotes migration of tumor cells to adipocyte-rich areas and **(8)** accelerates absorption of lipids by tumor cells to make up for the insufficient glucose supply in tumor tissues. The dotted arrow indicates putative roles of galectin-3 that needs further investigation for confirmation.











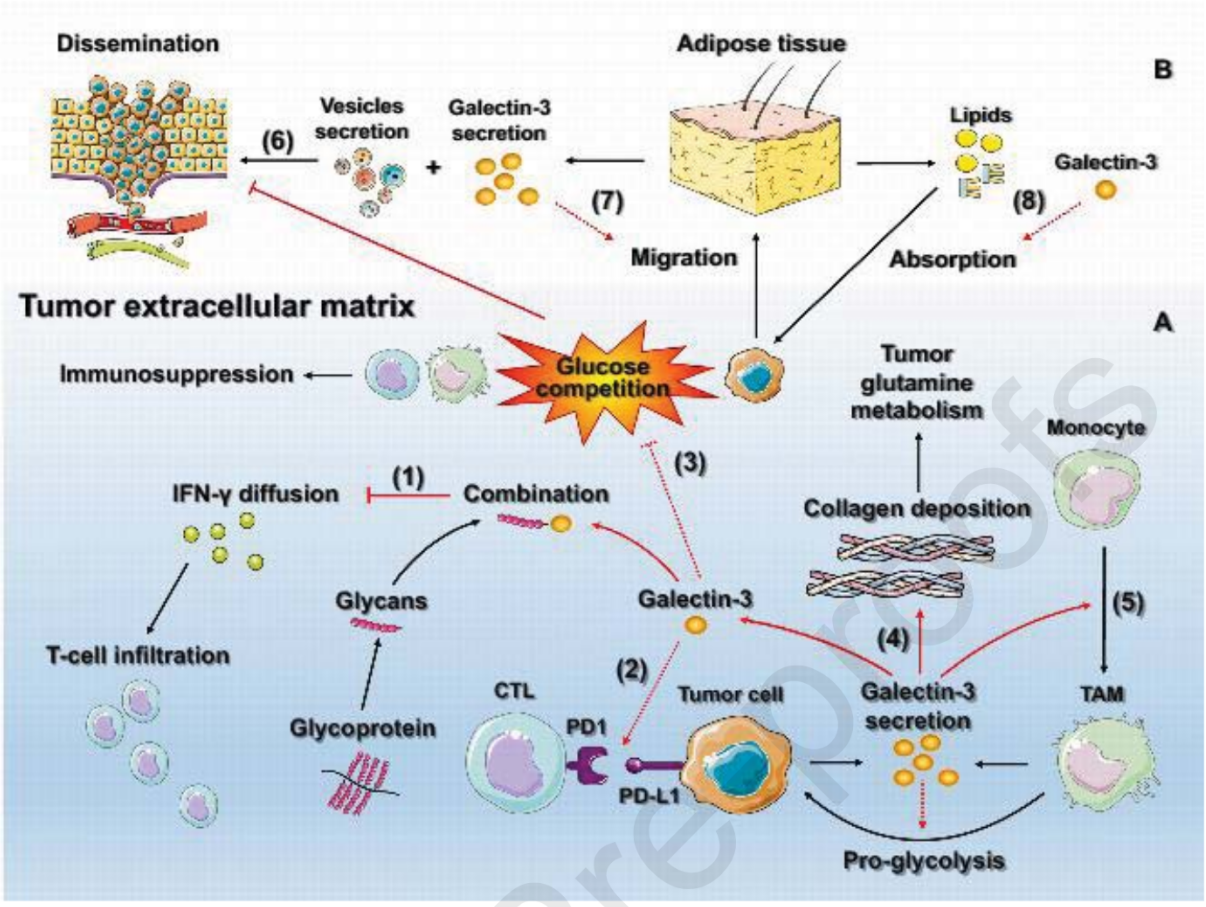


Table 1. Role of galectin-3 in diabetes and obesity

Impact of diseases	Targets	Affected factors	Consequences	Ref.
Diabetes (+)	IR	Insulin sensitivity; Insulin signaling; Glucose transport; Macrophages chemotaxis and accumulation	Accelerating Cellular and systemic insulin resistance; Leading to glucose intolerance and adipose tissue inflammation	[33-35]
Diabetes (-)	AGE, ALE, GLUT1/4	Blood glucose; insulin and HbAIc levels	Maintaining blood glucose and pressure levels; Reducing endothelial damage; Improving harmful immune responses and metabolic disorders caused by diabetes	[25-29]
Obesity (+)	CPT1A, OPN, CCL2	Differentiatiion of adipocytes; Fibroblast proliferation; TG; LPC; Body weight; eWAT mass	Accelerating fibrosis and adipose tissue inflammation; Leading to cardiac lipotoxicity; Aggravating LV dysfunction，mitochondrial dysfunction and metabolic dysfunction in obesity	[27,41, 48,49, 53-55]
Obesity (-)	PPAR-γ, FABP4, ATGL	Content of visceral adipose tissue; Body weight	Improving excessive obesity; Maintaining stable blood glucose; Fighting systemic inflammation in obese patients	[26,27, 40]

(+): promote disease progression; (-) inhibit disease progression; IR: insulin receptor; AGE: advanced glycosylation end product; ALE: lipid peroxidation end product; GLUT: glucose transporter; HbAIc: glycated hemoglobin; CPT1A: carnitine palmitoyltransferase I A; OPN: osteopontin; CCL2: chemokine (C-C motif) ligand 2; TG: total triglyceride; LPC: lysophosphatidyl choline; eWAT: white adipose tissue of the epididymis; LV: left ventricular; PPAR: peroxisome proliferators-activated receptor; FABP: fatty acid-binding protein; ATGL: adipose triglyceride lipase.